

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

04-11912 NG

CHARLOTTE CZWAKIEL, and
RAYMOND CZWAKIEL

Plaintiffs

vs.

WYETH, INC.; WYETH
PHARMACEUTICALS, INC.;

Defendants.

Docket No.

MAGISTRATE JUDGE

COMPLAINT
AND JURY DEMAND

RECEIPT # 58337
AMOUNT \$ 30
SUMMONS ISSUED yes
LOCAL RULE 4.1
WAIVER FORM
MCF ISSUED
BY DPTY. CLK. TCM
DATE 9-1-04

For their Complaint for personal injury caused by Defendants' prescription hormone replacement therapy (hereafter "HRT" or "HT"), Plaintiffs allege and aver as follows:

I. INTRODUCTION

1. Defendants Wyeth, Inc. and Wyeth Pharmaceuticals, Inc. (hereinafter "Wyeth") tested, manufactured, marketed, distributed, promoted, and sold Premarin, Prempro, Premphase, and medroxyprogesterone acetate (synthetic progestin). Prempro, Premphase and Premarin are hormone replacement drugs prescribed for post-menopausal women to treat some of the problems often associated with menopause, such as hot flashes, night sweats, sleeplessness, and vaginal dryness. Medroxyprogesterone acetate is the synthetic progestin used in Prempro and Premphase.

2. Premarin is referred to as "estrogen only," "estrogen replacement," or

“unopposed estrogen” hormone therapy because Premarin pills contain only estrogen.

3. Prempro and Premphase are referred to as “combination” hormone therapy because progestin is added to the estrogen. Prempro combines the two hormones, estrogen and progestin, in a single tablet that is taken daily, while Premphase adds progestin to the daily dosage of estrogen only during the last two weeks of the menstrual cycle.

4. When Premarin is taken concurrently with the synthetic progestin medroxyprogesterone acetate (“MPA”), the combination hormone therapy is pharmacologically similar to Prempro.

5. For decades, Wyeth has vigorously promoted the hormone replacement therapy it marketed as safe, efficacious and beneficial to women.

6. Likewise, other hormone therapy manufacturers, such as those named herein, have promoted their synthetic estrogen and/or progestin hormone therapy products as safe, efficacious and beneficial to women.

7. However, on July 9, 2002, the National Heart, Lung and Blood Institute (“NHLBI”), a division of the National Institutes of Health (“NIH”), prematurely halted the 16,600-patient Women’s Health Initiative (WHI study) clinical trial designed to evaluate the risks and benefits of Prempro hormone therapy in healthy post-menopausal women after WHI researchers determined the risks of taking Wyeth’s Prempro outweighed its benefits.

8. Almost simultaneously, researchers at the National Cancer Institute (“NCI”) reported that women who use long-term estrogen therapy (e.g., Wyeth’s Premarin) are at a significantly increased risk of developing ovarian cancer.

9. Taken together, the two studies established that long-term use of Wyeth's hormone therapy increased the risk of cardiovascular disease, invasive breast cancer, pulmonary embolism, blood clots, stroke, heart attack and ovarian cancer.

10. Wyeth knew, or should have known, the severe risks its hormone therapy posed to women. The decades-long marketing and promotion by Wyeth of hormone therapy - either as combination estrogen and progestin therapy (e.g., Prempro or Premphase) or estrogen alone (e.g., Premarin), as safe and beneficial to post-menopausal women was false and misleading.

11. The other hormone therapy Defendants named herein, also knew, or should have known, the severe risks their hormone therapy products posed to women.

II. PARTIES, JURISDICTION AND VENUE

12. Plaintiff, Charlotte Czwakiel is and at all times relevant hereto, a citizen and resident of Middlesex County, Massachusetts, residing at 15 Palomino Drive, Tyngsboro, Massachusetts.

13. Plaintiff, Raymond Czwakiel is and at all times relevant hereto, a citizen and resident of Middlesex County, Massachusetts, residing at 15 Palomino Drive, Tyngsboro, Massachusetts.

14. Plaintiff, Raymond Czwakiel, was at all times the spouse of Plaintiff, Charlotte Czwakiel and lived and cohabitated with Plaintiff Charlotte Czwakiel in Middlesex County Massachusetts.

15. Plaintiff, Charlotte Czwakiel was prescribed Prempro in approximately 1997 by Dr. Kennedy. On September 3, 2001 Plaintiff was diagnosed with a pulmonary embolism and/or blood clots.

16. This action is venued in this District under favor of 28 U.S.C. 1391.

17. Defendant Wyeth Pharmaceuticals, Inc., is a New York corporation with a principal place of business at 5 Giralda Farms, Madison, New Jersey and 500 Arcola Drive, Collegeville, Pennsylvania. At all times relevant hereto, Wyeth Pharmaceuticals, Inc., was engaged in the testing, manufacturing, labeling, marketing, distribution, promotion, and sale of hormone therapy drugs, including Premarin, Prempro, Premphase, and medroxyprogesterone acetate, in Minnesota.

18. Defendant Wyeth, Inc., is a Delaware corporation headquartered and with a principal place of business at 5 Giralda Farms, Madison, New Jersey and 500 Arcola Drive, Collegeville, Pennsylvania. At all times relevant hereto, Wyeth, Inc., was engaged in the testing, manufacturing, labeling, marketing, distribution, promotion, and sale of hormone therapy drugs, including Premarin, Prempro, Premphase, and medroxyprogesterone acetate in Minnesota.

19. The amount in controversy exceeds seventy-five thousand dollars (\$75,000.00) exclusive of costs and interest, and diversity jurisdiction exists under favor of 28 U.S.C Section 1332.

III. FACTUAL BACKGROUND

A. The Marketing of Hormone Therapy

20. Menopause is the cessation of menstruation caused by declining levels of estrogen and progesterone. It is a natural human phenomenon-- a phase of the female

reproductive aging process-- and is not a disease. Symptoms, which vary in severity from woman to woman, may include hot flashes, chills, vaginal dryness, headache and irritability. Adverse consequences of the drop in estrogen levels which begin with menopause and continue after menopause include, *inter alia*, vaginal atrophy and dryness; an increase in LDL cholesterol levels; and, a decrease in bone density with resultant increased risk of osteoporosis.

21. These symptoms and consequences of menopause have been described in scientific literature since the late 1800s, and by the turn of the 20th century the search for an aid to alleviate them was widely pursued.

22. In 1942, Ayerst, the predecessor to Wyeth, received patent and FDA approval for Premarin, a mix of estrogens extracted from the urine of pregnant mares. Premarin was marketed to women and their physicians as the long sought after replacement for lost estrogen in menopausal women, and was referred to as "Replacement" estrogen therapy.

23. The FDA originally approved Premarin only to relieve menopausal symptoms, such as hot flashes and vaginal atrophy. Wyeth, however, has long touted additional benefits for Premarin, and its subsequently marketed hormone therapy drugs, Prempro, Premphase and medroxyprogesterone acetate.

24. In the 1960's, Wyeth's Premarin promotional materials utilized articles and books written Dr. Robert Wilson, a Brooklyn, New York, gynecologist, who recommended uses of Premarin far beyond those approved by the FDA. In a 1962 article, which appeared in the *Journal of the American Medical Association (JAMA)*, Dr. Wilson claimed taking estrogen during menopause *reduced* breast and genital cancers.

In his 1966 best selling book entitled *Feminine Forever*-- which Wyeth's sales forces distributed to physicians throughout the country-- Dr. Wilson wrote that "aside from keeping a woman sexually attractive and potent . . . estrogen preserves the strength of her bones, the glow of her skin, the gloss of her hair . . . Estrogen makes women adaptable, even-tempered, and generally easy to live with." In the book, Dr. Wilson again asserted that estrogen prevented cancers.

25. Following Dr. Wilson's publications, sales of Premarin quadrupled. Wyeth poured thousands of dollars into Dr. Wilson's research. By the mid-70s, more than 30 million prescriptions for Premarin were being written every year, eventually making it the fifth most frequently prescribed drug in the United States.

26. Physicians were instructed in advertisements to prescribe Premarin to achieve "tranquilizing" effects for their female patients-- as if that effect was a laudable goal: "Almost any tranquilizer might calm her down . . . but at her age, estrogen may be what she really needs."

27. The promotional advertising downplayed the risks of hormone therapy and over promoted the benefits. A 1970's article in *Harper's Bazaar* claimed: "There doesn't seem to be a sexy thing estrogen can't and won't do to keep you flirtatiously feminine for the rest of your days . . . a real package deal that spruces up your vagina Prevalent medical opinion is that the safety and benefits of ERT have been convincingly demonstrated."

28. But the "safety and benefits" of Premarin were cast in serious doubt following the 1976 publication in the *New England Journal of Medicine* of a study evidencing a causal relationship between estrogen and endometrial cancer. Sales

plummeted, and physicians stopped prescribing Premarin except to those women who had hysterectomies and thus were not at risk for endometrial cancer.

29. A 1980 medical article suggested a solution. Dr. Don Gambrell reported in the journal *Obstetrics and Gynecology* that adding progestin to estrogen led to a *decline* in endometrial cancer. Wyeth thus produced and marketed progestin (i.e., synthetic progesterone or medroxyprogesterone acetate) as an adjunct to Premarin estrogen hormone therapy to protect against the risk of endometrial cancer.

30. Wyeth does now and has manufactured, marketed, and distributed medroxyprogesterone acetate for use in combination with Premarin under trademarked brand names such as Provera and Cycin and as generic equivalents. And, Prempro and Premphase have the added synthetic progesterone.

31. Additional claims were made in the 1980's when Wyeth promoted hormone therapy to help prevent bone loss, and when Wyeth claimed that hormone therapy drugs could prevent cardiovascular disease. By claiming that hormone therapy drugs prevented osteoporosis and cardiovascular disease, Wyeth was able to promote Premarin as recommended treatment for all women, whether or not they were experiencing menopause. As a result, between 1990 and 1995 Premarin became the most frequently dispensed prescription drug in the United States.

32. Premarin's huge success was bolstered by claims that indefinite, long term use of estrogen therapy was safe and efficacious. In an early 1990's promotional videotape distributed directly to consumers entitled "What every woman should know about estrogen," Wyeth represented to women that estrogen provided "long term health protection" and should be continued indefinitely, even after short-term menopausal

symptoms, such as hot flashes, had subsided. When a purported consumer inquired how long Premarin should be taken, Wyeth's doctor-spokesperson responded "anywhere from five to ten years in order to get protection from long term problems." And, with regard to breast cancer risks, Wyeth represented to women that the benefits of taking estrogen "far outweigh[ed]" the risks for women unless they faced a particularly high risk of breast cancer.

33. Prior to 1995, Wyeth began to develop a combination therapy pill that would combine Premarin with progestin. This product development was necessary since Wyeth was faced with the threat of a shrinking market for Premarin at the end of its patent protection in 1995.

34. In 1995 Wyeth introduced Prempro and Premphase, "combination" hormone therapies that contained estrogen and medroxyprogesterone acetate (synthetic progestin).

35. Physicians and females were led by Wyeth to believe the promotional claims it made regarding Premarin. When Prempro and Premphase were introduced to the market by Wyeth, physicians and women were led to believe that the same claims existed for these hormone therapies as Wyeth had claimed about Premarin.

36. Wyeth over-promoted Prempro and Premphase just as it did Premarin. For example, Wyeth distributed a brochure that asked women to "Take a few minutes to think about the rest of your life," and then listed medical conditions to "think about," which neither Prempro nor Premarin had been approved by the FDA to treat, including Alzheimer's disease, vision problems, tooth loss, heart disease, and colon cancer.

37. In a magazine advertisement featuring model Lauren Hutton, Wyeth made

a rash of similar claims, suggesting that its hormone therapy drugs were appropriate for treating or preventing, among other things, memory loss, colon cancer, and age-related vision loss. In the March 19, 2000, edition of *Parade Magazine*, Wyeth spokesperson Lauren Hutton (who was not identified as a Wyeth spokesperson) was asked what she did to look good and feel fit, and she answered: “[M]y number one secret is estrogen. It’s good for your moods; it’s good for your skin. If I had to choose between all my creams and makeup for feeling and looking good, I’d take the estrogen.

38. Wyeth’s DTC (i.e., “direct-to-consumer” or “DTC” marketing) efforts have included overt advertising pieces, such as print advertisements, videotapes, and brochures directed to consumers, as well as “product placement” efforts in which hormone therapy drugs are favorably positioned in entertainment vehicles or favorably described in the popular press by hired spokespersons

39. Wyeth has vigorously promoted hormone therapy to physicians, as well as to consumers directly. In 1999, Wyeth spent \$34.7 million on DTC advertising for Prempro. In 2000, Wyeth spent \$37.4 million on Prempro DTC advertising. The thrust of Wyeth’s marketing efforts has been to create a lifelong consumer demand for hormone therapy, and a belief by physicians that the prescription is beneficial to menopausal and post-menopausal patients.

B. The WHI and NCI Studies

40. Wyeth’s promotion of hormone therapy for long-term use proved false and misleading when studies released in July 2002 showed that such use substantially increases the risk of *causing* disease.

41. Two large cohort studies concluded that the risks of hormone therapy outweighed the benefits for most women: The WHI study, reported at Roussow JE, et al., *Risks and Benefits of Estrogen Plus Progestin in Healthy Post-menopausal Women*. (JAMA. 2002 Jul 17; 288:321-33.); and, the NCI study, reported at Lacey JV Jr., et al., *Menopausal hormone replacement therapy and risk of ovarian cancer*. (JAMA. 2002 Jul 17; 288(3):334-41.)

42. The Women's Health Initiative (WHI) is a group focused on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in post-menopausal women. Between 1993 and 1998, the WHI enrolled 161,809 post-menopausal women in the age range of 50 to 79 years into a set of clinical trials and an observational study at 40 clinical centers in the United States. Included within the clinical trials was a study by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

43. Participants in the NHLBI component of WHI, like most women with a uterus who take hormone therapy, were given progestin in combination with estrogen (i.e., combination hormone therapy). The estrogen plus progestin trial of the WHI involved 16,608 women ages 50 to 79 years with an intact uterus. An important objective of the trial was to examine the effect of estrogen plus progestin on the prevention of heart disease and hip fractures, and any associated change in risk for breast and colon cancer. The study did not immediately address the short-term risks and benefits of hormones for the treatment of menopausal symptoms.

44. Women enrolled in the estrogen plus progestin study were randomly assigned to a daily dose of estrogen plus progestin (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate) or to a placebo. Those participants receiving the drug (not placebo) received Wyeth's drug Prempro. Participants were enrolled in the study between 1993 and 1998 at over 40 clinical sites across the country.

45. In 2000 and again in 2001, WHI investigators complied with a recommendation from the study's Data and Safety Monitoring Board (DSMB) to inform participants of a small increase in heart attacks, strokes, and blood clots in women taking hormones. The DSMB, an independent advisory committee charged with reviewing results and ensuring participant safety, found that the actual number of women having any one of these events was small and did not cross the statistical boundary established to ensure participant safety. Therefore, the group recommended continuing the trial due to the still uncertain balance of risks and benefits.

46. At the DSMB's meeting on May 31, 2002, the data review revealed for the first time that the number of cases of invasive breast cancer in the estrogen plus progestin group had crossed the boundary established as a signal of increased risk. The DSMB's May 31, 2002, recommendation to stop the trial was based on the finding of increased breast cancer risk, supported by the evidence of overall health risks exceeding any benefits. On July 8, 2002 participants started receiving letters informing them about the results and telling them that they should stop study medications.

47. The WHI Study found that for the estrogen plus progestin group (i.e., those women who took Prempro) compared to placebo, overall there was a:

- (i) 41 percent increase in strokes,
- (ii) 29 percent increase in heart attacks,
- (iii) a doubling of rates of venous thromboembolism (blood clots),
- (iv) 22 percent increase in total cardiovascular disease,
- (v) 26 percent increase in breast cancer,
- (vi) a 37 percent reduction in cases of colorectal cancer, and
- (vii) a one-third reduction in hip fracture rates.

48. The WHI Study concluded that the “Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy post-menopausal US women.” The Study also found that the combination hormone regimen should not be initiated or continued for primary prevention of coronary heart disease.

49. Because of the importance of the report from the WHI investigators on the estrogen plus progestin study, the study was released early to the public on July 9, 2002, as an expedited article on the *JAMA* Web site. In commenting on the studies findings, NHLBI Director, Dr. Claude Lenfant, was unequivocal in his own conclusions:

The cardiovascular and cancer risks of estrogen plus progestin outweigh any benefits—and a 26 percent increase in breast cancer risk is too high a price to pay, even if there were a heart benefit. Similarly, the risks outweigh the benefits of fewer hip fractures.

50. Dr. Jacques Roussow, acting director of the WHI and lead author of the *JAMA* article, summarized the risks of combination hormone therapy in a very straightforward manner as he explained the statistical significance of the study results:

The WHI results tell us that during 1 year, among 10,000 post-menopausal women with a uterus who are taking estrogen plus progestin, 8 more will have invasive breast cancer, 7 more will have a heart attack, 8 more will have a stroke, and 18 more will have blood clots, including 8 with blood clots in the lungs, than will a similar group of 10,000 women not taking these hormones. This is a relatively small annual increase in risk for an individual woman. Individual women who have participated in the trial and women in the population who have been on estrogen and progestin should not be unduly alarmed. However, even small individual risks over time, and on a population-wide basis, add up to tens of thousands of these serious adverse health events.

(Emphasis added.)

51. Within a week after the WHI results were reported, another article appeared in JAMA related to the risk of long-term use of estrogen-only therapy. On July 17, 2002, JAMA published a NCI study, which found that women who took estrogen were more likely to develop ovarian cancer than those not on the hormone.

52. In the study, researchers from the NCI followed 44,241 women for 19 years who were taking estrogen only and found that these women had a 60% higher risk of ovarian cancer than women who had never used estrogen. The risk increased proportionately with longer duration of estrogen use. Women who took estrogen for 10 to 19 years had an 80% higher risk than those who did not take the pills. Those on the hormone therapy for 20 years or more were three times as likely to develop ovarian cancer as women who did not take it at all. Most of the NCI participants used Wyeth's brand of estrogen therapy, Premarin.

53. Lead author of the NCI study, James V. Lacey, summarized the results of his study with the following statement:

The main finding of our study was that post-menopausal women who used estrogen replacement therapy for 10 or more years were at significantly higher risk of developing ovarian cancer than women who never used hormone replacement therapy.

54. Dr. Lacey further underscored the implications of his NCI study, by explaining that the findings translate into one or two additional ovarian cancers each year per 10,000 women taking estrogen alone. In 2000, eight million American women took Premarin, the leading estrogen therapy pill. The Lacey study demonstrates that Premarin usage is responsible for up to 1,600 additional ovarian cancer cases in the year 2000 alone.

55. In October 2003, the WHI study produced a report with findings similar to the NCI study regarding ovarian cancer. The October 1, 2003, issue of JAMA reported that combination hormone therapy was also associated with increased risk for ovarian cancer: the WHI investigators found that women randomized to receive combined hormone therapy (i.e., estrogen plus progestin) experienced a 58% increase in ovarian cancer rates.

C. The Aftermath of the WHI and NCI Studies

56. The WHI and NCI studies received enormous media coverage: front-page newspaper headlines, magazine covers, and broadcast news programs urgently reported the alarming and significant findings.

57. Commenting on the WHI study, Dr. Leslie Ford, associate director for clinical research at the NCI's Division of Cancer Prevention, re-emphasized the risk of hormone therapy to patients:

The reduction in colorectal cancer risk in the WHI is intriguing, but the balance of harm versus benefit does not justify any woman beginning or continuing to take estrogen plus progestin for this purpose.

58. Dr. Isaac Schiff of Massachusetts General Hospital also commented on the WHI study, noting, "Quality of life is very, very important From a heart and breast cancer point of view, the drug should be outlawed. But for hot flashes, there's nothing better."

59. The WHI and NCI study conclusions regarding the unsafe and dangerous adverse effects of hormone therapy have been verified by subsequent published research. A study on hormone therapy and breast carcinoma risk in Hispanic and non-Hispanic women, reported on September 1, 2002, in the journal *Cancer*, found that that Hispanic post-menopausal women have significantly increased breast cancer risk after long-term hormone therapy.

60. On October 23, 2002, the United Kingdom's Medical Research Council announced that it had ended a clinical study of the risks and benefits of long-term use of hormone therapy for "scientific and practical reasons." 5,700 women were enrolled in the "WISDOM" study (the Women's International Study of Long Duration Oestrogen after Menopause). The study was to include 22,000 women. However, following the WHI study, the WISDOM study was canceled. The Medical Research Council concluded "There is strong evidence that taking hormone therapy long term increases the risks of some diseases such as breast cancer and decreases the risks of others such as osteoporosis."

61. Because of the significance of its findings, on March 17, 2003, the New England Journal of Medicine (NEJM) released a follow-up WHI study two-months in advance of its May 8th publication date. The follow-up study reported that hormone therapy failed to improve the quality of life for menopausal women.

62. The Quality of Life study which examined the same pool of 16,000 women as the July 9, 2002, WHI study, found that hormone therapy drugs do not do the very thing many women took them for in the first place— that is, to make them feel happier and healthier after menopause. A comparison of women who took hormone therapy to women given a placebo showed those women taking hormones did not report sleeping better or feeling better. The hormone therapy group also did not report less depression or more sexual satisfaction than the placebo group.

63. According to the study's lead author, Dr. Jennifer Hays: "It's just not something that's going to make most women feel better. Even if it reduces your symptoms, that's not going to translate into a meaningful effect on a quality of life." Dr. Deborah Grady of the University of California, San Francisco, in an accompanying commentary in the same issue of the NEJM said that: "There is no role for hormone therapy in the treatment of women without menopausal symptoms" and that only women who were experiencing debilitating menopausal symptoms should take hormone therapy. She stated that those women who do continue with hormone therapy should take the lowest possible dose for the shortest possible time.

64. On May 21, 2003, JAMA published another study studying the efficacy of estrogen plus progestin therapy (e.g., Prempro) for prevention of bone loss in elderly women. The study involved 373 women ages 65 to 90 who had either thinning bones or

full-blown osteoporosis and took one of four treatments for three years: (i) combination hormone therapy alone, (ii) a bone-building drug, alendronate (which is sold under the brand name, Fosamax), (iii) combination hormone therapy with Fosamax, or (iv) a placebo.

65. While the study found that the combination of hormone therapy and Fosamax was effective at treatment and prevention of post-menopausal osteoporosis, it also concluded that Fosamax alone was more effective than combination hormone therapy alone. After three years, hip bone density had increased nearly 6 percent in women on hormone therapy with Fosamax, 4 percent in those on Fosamax alone, and 3 percent in the hormones-only group.

66. Dr. Jennifer Hays, a WHI researcher and lead author of the May 8, 2003, JAMA study on hormone therapy and quality of life, said that the findings of the bone-loss study are not convincing enough to recommend hormone therapy for osteoporosis prevention even in older women, especially because the study showed that the bone-enhancing benefits from estrogen come only after long-term use which also carries the highest risk of breast cancer or heart disease.

67. On May 28, 2003, JAMA published yet another study on the effects of hormone therapy, this time focusing on the risk of Alzheimer's disease and other types of dementia. The study found that combination hormone therapy, consisting of both estrogen and progestin, doubled the risk of dementia for woman who started hormones at age 65 or older.

68. The dementia study was based on a four-year experiment involving 4,532 women at 39 medical centers, where half took placebos and half took Prempro. In four

years, there were 40 cases of dementia in the Prempro group and 21 in the placebo group. Translated to an annual rate for the population-at-large, the results mean that for every 10,000 women 65 and older taking hormone therapy, there will be 45 cases of dementia a year with 23 of them attributable to hormone use.

69. Dr. Sally A. Shumaker, the director of the dementia study and a professor of public health sciences at Wake Forest University, stated that the study's "clear message is that there's no reason for older women to be taking combination hormone therapy."

70. On June 25, 2003, JAMA published still another study analyzing the data from the Women's Health Initiative, which found that in addition to stimulating the growth of breast cancer, combination hormone therapy makes breast tumors harder to detect, leading to dangerous delays in diagnosis. The report found that breast abnormalities could develop soon after a woman starts taking hormone therapy. Consequently, the study's findings raise questions about the safety of even short-term hormone use. In the same June 25, 2003, issue that reported this study, JAMA also published an editorial by Dr. Peter H. Gann, a cancer epidemiologist at Northwestern University, who stated that this study represents "further compelling evidence against the use of combination estrogen plus progestin hormone therapy."

71. The connection between hormone therapy usage and breast cancer found in the WHI studies were confirmed by a similar study conducted in the United Kingdom. The August 9, 2003, issue of *Lancet* reported on the conclusions reached by *The Million Women Study* — a major research effort funded by Cancer Research UK — confirming that current and recent use of hormone therapy increases a woman's chance

of developing breast cancer, and that the risk increases with duration of use. Scientists at the Cancer Research UK analyzed data from over one million women between the ages of 50 and 64. Researchers found that post-menopausal women using combination hormone therapy were twice as likely to develop breast cancer as non-users (a 100 per cent increase).

72. In the August 7, 2003, issue of *NEJM*, the WHI study continued to yield important information regarding the safety of hormone therapy use. The study found that combination hormone therapy does not protect the heart and may even increase the risk of coronary heart disease (CHD). Specifically, the WHI study found that combination hormone therapy usage was associated with a 24% overall increase in the risk of CHD (6 more heart attacks annually per 10,000 women using combination therapy) and a 81% increased risk of CHD in the first year after starting combination therapy.

73. In addition to the studies published in *JAMA*, *NEJM*, and other medical journals, a recent federal agency report also revealed that estrogen could be dangerous to women taking it as hormone therapy. On December 11, 2002, the National Institute of Environmental Health Sciences released its tenth annual report on carcinogens, which declared for the first time that estrogen is now on the federal government's list of "known human carcinogens."

D. Wyeth Changes Hormone Labels and Reverses Long-Term Marketing Strategy

74. In light of the WHI and NCI studies and other subsequent research reports, the labels provided by Wyeth for its Premarin and Prempro drugs were

inadequate, misleading, and inaccurate. In fact, Wyeth changed warning labels on Premarin and Prempro during the last week of August 2002 to reflect the results of the July 2002 WHI and NCI studies.

75. Prior to the label change in August 2002, the Premarin warning label made no mention whatsoever of ovarian cancer.

76. The Prempro label warnings were likewise inadequate prior to August 2002. As to breast cancer, the Prempro warning explains the risk of breast cancer with conjugated estrogens (the Premarin component of Prempro), but then adds, with regard to the effect of added progestins on the risk of breast cancer: "The overall incidence of breast cancer does not exceed that expected in the general population." The WHI study plainly reveals that this warning is false and was known or should have been known by Wyeth to be false for decades.

77. The Prempro warnings were also inadequate for two thromboembolic disorders, pulmonary embolisms and blood clots: "The increased risk [of venous thromboembolism] was found only in current ERT [i.e., Premarin only] users." Furthermore, as to cardiovascular disease (heart attacks and strokes), the Prempro warning reads simply "Embolic cerebrovascular events and myocardial infarctions have been reported," without disclosing the true nature of the risk.

78. Under precautions, the Prempro label acknowledges: "The effects of estrogen replacement therapy on the risk of cardiovascular disease have not been adequately studied." Nevertheless, Wyeth has long promoted the supposed benefits of long term hormone therapy for cardiovascular disease.